REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view the amendments and remarks herein, is respectfully requested. Claims 153-154 and 169 are amended. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims present prior to the amendments herein, which claims are in a continuing application of the above-identified pending application. Claims 153-155 and 157-173 are now pending.

The Non-Statutory Obviousness-Type Double Patenting Rejection

Claims 153-173 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 173-194, 196-203, 205-211, and 231 of copending application Serial No. No. 09/754,775. Applicant notes that the '775 application has not yet issued and is pending. Therefore, a terminal disclaimer is not required until issuance of that application or the present application. If a terminal disclaimer is required, it can be requested by the Office as a condition of allowance.

The 35 U.S.C. § 112 Rejection

Claims 153-155 and 157-168 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. This rejection is respectfully traversed.

In particular, the Examiner asserts that the specification does not reasonably provide enablement for preventing a vascular indication in a mammal. However, Example 7 discloses that adult C57B16 mice were fed a normal or high fat diet ± tamoxifen (TMX), a TGF-beta elevating agent. As shown in Table 2, TMX administration reduced the number and size of lesions in those mice. Therefore, TGF beta elevating agents like TMX can prevent vascular disorders. Nevertheless, to advance the application, claims 153-154 are amended to delete "preventing."

Thus, withdrawal of the § 112(1) rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 153-155, 157-159, 164-165, and 168 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)) in view of Ellis et al. (U.S. Patent No. 4,826,876). Claims 153-155, 157-159, 164-165, and 168 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gylling et al. (Atherosclerosis, 96:245-247 (1992)) in view of Ellis et al. Claims 153-155, 157-162, 165, and 169-172 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. (WO 94/09764) and Schilling (Therapiewoche, 25:1157 (1975)) in view of Knabbe et al. (Am. J. Clin. Oncol., 14:S15 (1991)) and further in view of Kangas (Breast Cancer Res. Treat, 16:S3 (1990)). Claims 153-155, 157-162, 165, and 169-172 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941) in view of in view of Knabbe et al. and further in view of Kangas. Claims 163 and 173 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. and Schilling in view of Kangas and further in view of Knabbe et al. and Warri et al. (J. Natl. Cancer Inst., 85:1412 (1993)). Claims 166-168 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. and Schilling in view of Kangas and further in view of Knabbe et al. and Grainger et al. (Biochem. J., 294:109 (1993)). Claims 153-155 and 169 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Connolly et al. (U.S. Patent No. 5,250,561). These rejections are respectfully traversed.

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was administered to female rats (page 1 of the translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day. These amounts were based on earlier studies where a 0.7 mg/mL group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada et al. at page 13. Based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF-beta levels, whether it is due to the toxicity of toremifene, or if it is due to

the decrease in feed consumption. Moreover, Sawada et al. do not disclose or suggest that toremifene administration lowers LDL-cholesterol ("bad" cholesterol) or does not have an adverse effect on "good" cholesterol.

Given that the amounts of toremifene administered to healthy rats in Sawada et al. resulted in weight gain suppression in the 0.01 mg/kg and 1 mg/kg groups, reduced feed consumption in the 0.01 mg/kg, 0.1 mg/kg and 1 mg/kg groups, an abnormal estrous cycle in the 0.1 mg/kg and 1 mg/kg groups, and abnormal blood chemistry in the 1 mg/kg group and 10 mg/kg group, Sawada et al. teach away from the use of toremifene for indications other than cancer. That is, one of skill in the art in view of Sawada et al. would recognize that anti-breast cancer effect of toremifene outweighs the undesirable effects disclosed in Sawada et al. but that the benefit of toremifene administration to treat noncancerous indications may be outweighed by those undesirable effects.

Ellis et al. relate to chemical compounds such as 3,5-dibromo-3'-[6-oxo-3(1H)-pyridazinyl-methyl]-thyronine that have selective thyromimetic activity (abstract). Ellis et al. disclose that antihyperlipidaemic agents that lower the LDL-cholesterol to HDL-cholesterol ratio are indicated as antiatherosclerotic agents.

With regard to the rejection of claims 153-155, 157-159, 164-165, and 168 over Sawada et al. and Ellis et al., neither Sawada et al. nor Ellis et al., alone or in combination, teach or suggest selecting or determining an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen and selecting a cytostatic dose of the agent for administration. Moreover, as Sawada et al. disclose that toremifene administration resulted in a total cholesterol reduction, as well as other undesirable side effects in female rats, Sawada et al. teach away from the use of toremifene for noncancerous indications because toremifene administration may lower HDL-cholesterol ("good" cholesterol). Further, assuming for the sake of argument that the 0.1 mg/kg dose or the 10 mg/kg dose is cytostatic (posited by the Examiner on page 8 of the Office Action), Sawada et al. teach away from the use of cytostatic doses of toremifene for noncancerous indications as those doses result in undesirable side effects.

Gylling et al. studied cholesterol synthesis in a woman with breast cancer before and during tamoxifen (TMX) treatment. The authors of Gylling et al. conclude that TMX inhibits

cholesterol synthesis, resulting in an increase in the cholesterol precursor Δ^8-cholesterol, which has harmful side effects (page 246). Gylling et al. also disclose that toremifene inhibited cholesterol synthesis in animal experiments (page 245).

With respect to the rejection of claims 153-155, 157-159, 164-165, and 168 in view of Gylling et al. and Ellis et al., neither Gylling et al. nor Ellis et al., alone or in combination, disclose or suggest selecting or determining an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen and selecting a cytostatic dose of the agent for administration. Further, Gylling et al. teach away from the use of agents such as TMX and toremifene in noncancerous indications, due to the harmful side effects to cholesterol synthesis observed with TMX and toremifene administration.

Ito et al. disclose the use of toremifene to treat autoimmune diseases. In particular, it is disclosed that the administration of 100 mg/kg toremifene orally every day for 13 weeks to mice with spontaneous autoimmune disease (MRL/Mp-lpr/lpr mice) inhibited the appearance of autoreactive T cells (page 8, Example 1). The only data shown in Example 1 is for spleen weight, lymph node weight, pathology of glomeruli, salivary gland, kidney and knee joint, and blood urea nitrogen. Example 2 in Ito et al. discloses twice a day administration of toremifene at 15 mg/kg or 30 mg/kg to MRL/Mp-lpr/lpr mice. Autoimmune diseases are degenerative diseases where the body's immune system destroys tissues (see page 191 of Churchill's Medical Dictionary, Churchill Livingstone, Inc., New York, NY (1989), a copy is enclosed herewith).

The amount of toremifene administered in Example 1 of Ito et al. is 10 times that of the highest "cytostatic" (according to the Examiner) dose administered to rats in Sawada et al., and that amount is administered to a smaller animal (mice). Interestingly, Kubo et al. (Proc. Natl. Acad. Sci. USA, 81:5831 (1984); a copy is enclosed herewith) report that reduced food intake alone doubles and even triples the life span and delays development of glomerulonephritis and maintained certain immunological responses in MRL/Mp-lpr/lpr mice. Similar results regarding feed intake and disease suppression for NZB x NZW mice (Example 3 in Ito et al. discloses toremifene administration at 3 mg/kg/day or 30 mg/kg/day three times per week to NZB x NZW mice) are provided in Gajjar et al. (J. Nutrition, 17:1136 (1987), a copy is enclosed herewith). Since toremifene administration to rats at lower doses than employed in Ito et al. resulted in

reduced feed intake (Sawada et al.), the results reported in Ito et al. showing disease improvement may ultimately have been due to reduced feed intake.

Schilling discloses that immune vasculitis is a group of inflammatory vascular diseases associated with antigen-antibody complexes in small to averaged sized arteries.

Knabbe et al. report that that addition of droloxifene, TMX and toremifene to MCF-7 breast cancer cells, induces TGF-beta.

Kangas reviews the pharmacological properties, safety, pharmacokinetics and clinical developments for toremifene as a breast cancer chemotherapeutic.

Warri discloses that, in breast cancer cells, toremifene increases TGFβ1 and promotes apoptosis.

And while Grainger et al. speculate that TMX may be useful to elevate TGF-beta in patients undergoing therapeutic angioplasty, the conclusions in Grainger et al. are specific to VSMCs and TMX.

In response to the rejection of claims 153-155, 157-162, 165, and 169-172 over Ito et al., Schilling, Knabbe et al. and Kangas, the Examiner is requested to consider that none of Ito et al., Schilling, Knabbe et al. or Kangas, alone or in any combination, disclose or suggest administering or identifying a cytostatic dose of an agent for TGF-beta elevation, which agent has reduced estrogenic activity or DNA adduct formation relative to tamoxifen. Moreover, neither Warri nor Grainger et al. remedy those deficiencies. Further, Warri teaches away from the use of toremifene in conditions where apoptosis is undesirable, e.g., in conditions other than cancer.

Yang discloses methods to identify agents for the treatment of osteoporosis or serum lipid lowering. The method includes the use of eukaryotic cells having a promoter region of a TGF-beta gene that is a raloxifene responsive element (column 7, lines 16-32). The method identifies agents that induce expression from a raloxifene responsive element without inducing deleterious side effects associated with current anti-osteoporosis therapy regimes (abstract). The results in Table 1 show that estradiol, raloxifene and tamoxifen induced expression from TGF-beta2 and TGF-beta3 derived promoters, not from TGF-beta1 derived promoters, that were present in human osteosarcoma cells (MG63 cells). The remaining agents were screened on cells with

TGF-beta3 derived promoters, i.e., MG63 cells, CHO (Chinese hamster ovary) cells or MCF-7 (breast cancer) cells.

With respect to the rejection of claims 153-155, 157-162, 165, and 169-172 over Yang, Knabbe et al. and Kangas, there is no combination of Yang et al. (a screening method which uses a vector with a raloxifene responsive element), Knabbe et al. and Kangas that discloses or suggests administering or identifying a cytostatic dose of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen. And the disclosure in Yang that toremifene induces TGF-beta secretion in human fetal fibroblasts in the absence of the estrogen receptor does not provide any disclosure or suggestion related to the use of a cytostatic dose of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, or increase plaque stability in a mammal.

Connolly et al. disclose compounds that inhibit HMG CoA reductase and cholesterol biosynthesis and their use to treat or prevent hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

Connolly et al. do not disclose or suggest administering a cytostatic dose of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen or to identifying a cytostatic dose of an agent for TGF-beta elevation that has reduced estrogenic activity of DNA adduct formation relative to tamoxifen.

The Examiner acknowledges that the references do not explicitly teach selecting a cytostatic dose, but alleges that such a dose is a parameter one of skill in the art would routinely optimize (page 15 of the Office Action). However, the Examiner has failed to consider that the art as a whole fails to disclose or suggest selecting agents that elevate TBG-beta and have reduced estrogenic activity or DNA adduct formation relative to tamoxifen, and identifying or administering a cytostatic dose of that agent. In particular, the Examiner has failed to consider that Sawada et al., Gylling et al. and Warri teach away from the use of at least structural analogs of TMX for noncancerous indications.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date March 11, 2008

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 11th day of March 2008.

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